Comparative genetics: **A third model nematode species**

Ralf J. Sommer

Recent studies have introduced *Oscheius* sp. CEW1 as a third nematode species accessible to genetic analysis, joining the better known *Caenorhabditis elegans* and *Pristionchus pacificus*. A group of vulva-defective mutants in *Oscheius* has been identified, with defects not seen in *C. elegans*.

Address: Max-Planck Institute for Developmental Biology, Abteilung für Evolutionsbiologie, Spemannstrasse 37-39, D-72076 Tübingen, Germany.
E-mail: ralf.sommer@tuebingen.mpg.de

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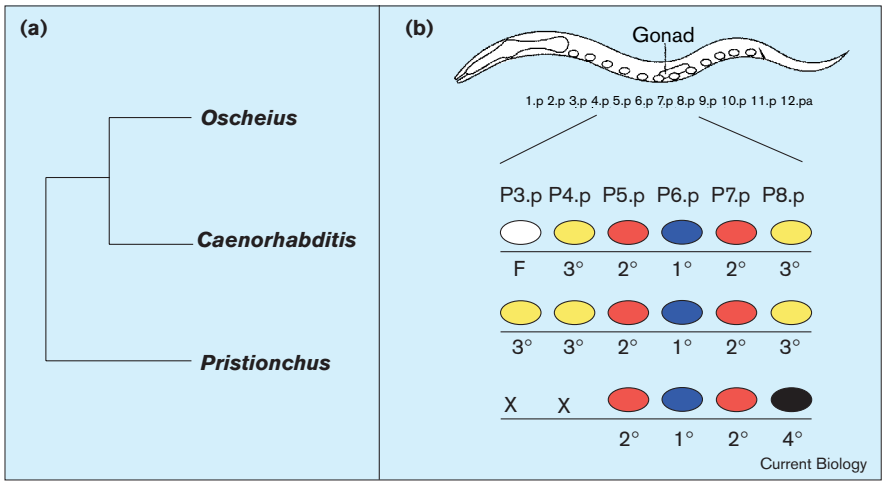
Much of our knowledge in developmental biology relies on the study of a limited number of model organisms. Often, these organisms have been chosen because they fulfill certain technical requirements, which allows them to be studied in the laboratory. Developmental genetics additionally requires fulfilment of other criteria, such as the ability to induce mutations and to isolate and culture mutant animals. Given these demands, only a handful of species are used in developmental genetics. Once a species is established as a model system, many additional genetic and molecular tools are added over time, resulting in a sophisticated toolkit specific to a particular model system.

But each model organism is just one particular species of a taxonomic group. The famous foursome of *Drosophila*, *Caenorhabditis elegans*, *Mus musculus* and *Arabidopsis thaliana* all have their own specific phylogenetic histories, resulting in morphological features that make them different from other insects, nematodes, mammals or higher plants. None of these organisms can be considered as a general representative of its group. Often, a particular process differs substantially between members of the same taxon. One example is insect segmentation, which has been well studied in *Drosophila*. The mechanisms of segment formation differ among insects in very basic respects: in *Drosophila*, all segments are formed simultaneously in a syncytial environment, whereas most insects develop segments sequentially in a cellular environment [1]. It is for such reasons that naturalists sometimes query the choice of particular model organisms. Would our understanding be different if another insect, another plant or another mammal had been originally chosen? The recent introduction [2] of a third nematode species, *Oscheius* sp. CEW1, as a new genetic model system illustrates how important the choice of a model organism really is.

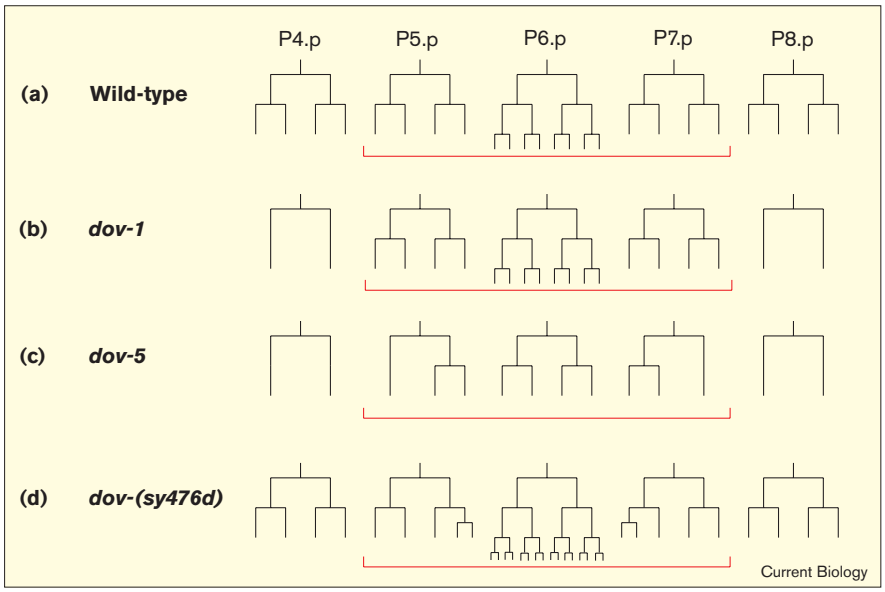
The free-living soil nematode *Caenorhabditis elegans* was introduced as a genetic model organism by Sydney Brenner only in the early seventies [3]. Since then, the advantages of the species for genetic, cell-lineage and molecular studies have made *C. elegans* one of the most important model systems for developmental biology and neurobiology. Within 30 years, work on *C. elegans* has taken our understanding of many developmental processes from a basic cellular description to detailed molecular mechanisms. These days, *C. elegans* is often just referred to as 'the worm'. But again, how general are many of the findings made in *C. elegans*? During the revival of evolutionary developmental biology in recent years, several

Figure 1



(a) Phylogenetic relationship of the three nematode species *Oscheius*, *C. elegans* and *P. pacificus*, based on ribosomal DNA sequence data. (Modified from [4].)
(b) A schematic diagram of the patterning and cell-fate specification in the ventral epidermis of nematodes. The 12 ventral epidermal cells, P(1–12).p, are equally distributed between pharynx and rectum. In all three species, P(5–7).p form vulval tissue with a 2°–1°–2° pattern. P(5,7).p form the outer cell fates (2°) and P6.p form the inner cell fates (1°). In *C. elegans*, P(3,4,8).p have a 3° cell fate and remain epidermal. After cell ablation of 2° and/or 1° cells, 3° cells can form part of the vulva. In *Oscheius*, P(4,8).p, but not P3.p, are vulval precursor cells, whereas in *P. pacificus* P(3,4).p die of programmed cell death.

Figure 2



Vulval cell lineages of *Oscheius* wild-type **(a)** and mutant animals **(b–d)**, as described by Dichtel *et al.* [2]. Vulval precursor cells undergo hypoproliferation or hyperproliferation without changing terminal vulval cell fates. Cells forming vulval tissue are underlined in red.

free-living nematodes other than *C. elegans* have been studied. Growing insight from these comparative studies also shed light on the generality of findings made with *C. elegans* as a model system.

Dichtel *et al.* [2] have now introduced *Oscheius* sp. CEW1 as a third nematode amenable to genetic analysis, in addition to *C. elegans* and *Pristionchus pacificus*. The phylogenetic relationships between free-living nematodes, including *Oscheius*, *C. elegans* and *P. pacificus*, are well established, primarily on the basis of ribosomal DNA sequences [4]. *Oscheius*, for example, is closely related to *C. elegans* but not to *P. pacificus*, which belongs to a different nematode family (Figure 1). The availability of three nematode species amenable to genetic analysis provides a unique platform for studying the genetic basis of the evolution of developmental processes.

One particular process that has been studied in great detail is the development of the vulva, the egg-laying structure and copulatory organ of nematode females and hermaphrodites. Over the last 20 years, studies on *C. elegans* vulva development have evolved from observing basic pattern formation to genetic suppression analysis to dissect the key intercellular signaling processes (for review see [5]). Building on this knowledge, comparative cell lineage studies showed that, in all the nematode species that have been studied, the vulva is a homologous structure formed from homologous precursor cells. Nonetheless, the cell–cell interactions among the vulva precursor cells vary between species (reviewed in [6]). Genetic studies in *P. pacificus* have also revealed that the function of homologous genes has changed during vulval evolution (reviewed in [7]).

The analysis of vulva-defective mutants in *Oscheius* led to a very surprising observation [2]. Mutations in 16 different genes were found to affect the cell-lineage pattern, but not the overall fate of the vulval precursor cells. In wild-type *Oscheius*, cells P(4–8).p form a 'vulva equivalence group', which means that all are intrinsically capable of contributing progeny cells to the vulva, and during normal development cells P(5–7).p adopt vulval fates with a 2°–1°–2° pattern (Figures 1,2a). The latter description uses the common terminology where 1° and 2° refer to the different vulval cell fates, varying in the nature of the vulval cells that they give rise to. Cells P4.p and P8.p have a 3° fate and remain epidermal.

Oscheius is unique among the nematode species that have been studied at this level of detail, in that the 2° and 3° cells have identical cell lineages: they all generate four progeny, which in the case of the 2° cells P(5,7).p participate in vulva formation, whereas the progeny of the 3° cells P(4,8).p fuse with the hypodermis (Figure 2a). P6.p, the cell that adopts the 1° cell fate, undergoes three rounds of cell divisions and generates eight progeny. Dichtel *et al.* [2] describe the isolation of mutants in which all or a subset of the vulval precursor cells undergo hypoproliferation or hyperproliferation, without changing the fate of the terminal vulval cells (Figure 2b–d). The number of terminal vulval cells varies between 10 and 26 in these mutants, whereas it is 16 in wild-type animals. These results suggest that the coupling of vulval differentiation and cell-cycle control is defective in these mutants, and that the terminal differentiation of vulval cells depends on a timing mechanism, rather than the round of cell divisions.

In principle it is not surprising that vulval-defective mutants should be found that exhibit hypoproliferation or hyperproliferation, as vulva differentiation, like any other developmental process, is coupled to cell-cycle control. For a long time, however, no such mutants were found in *C. elegans*. Just recently, Kipreos *et al.* [8] and Fay and Han [9] have described similar mutants of *C. elegans*, but they are by no means as common as they are in *Oscheius*. The *C. elegans* gene *cye-1* was identified in a clonal screen for sterile mutants, and its mutation results in hypoproliferation of vulval cells [9]; *cul-1* mutants have the opposite phenotype, with hyperproliferation of vulval cells [8]. So mutants affecting the coupling between the cell cycle and vulva differentiation can easily be obtained in *Oscheius*, but not in *C. elegans*. Some of these differences might result from redundancy of the developmental mechanisms in one, but not the other, species; but regardless of what causes the differences, the finding shows how the choice of a model organism really matters.

With the *Oscheius* data in mind, lets look back to Sydney Brenner's original choice. Why did Brenner pick *C. elegans*? In his original paper in *Genetics* [3], Brenner stated that he was looking for a system "suitable for genetic study and in which one could determine the complete structure of the nervous system". His choice was *C. elegans*, but it could equally well have been any other free-living hermaphroditic soil nematode. Comprehensive soil sampling indicates that hermaphroditic strains can readily be obtained from four nematode genera: *Caenorhabditis* and *Oscheius* of the Rhabditidae, and *Pristionchus* and *Rhabdontolaimus* of the Diplogastridae. *Rhabdontolaimus* is more difficult to culture than the other three, all of which fulfill the requirements for laboratory studies.

From the biogeographic distribution of these nematode species, *Oscheius* would have been the most obvious strain to start with, as *Oscheius* strains can be isolated from most soil samples around the world. Imagine if Brenner had picked *Oscheius* — a completely different set of vulva-defective mutants would then have been isolated. Taking for granted that the mutants described by Dichtel *et al.* [2] have something to do with cell-cycle control, one might hypothesize that cell-cycle control would have been an important issue in early work on the regulation of vulva formation. But the issue of cell-cycle control in vulva development in *C. elegans* has really gained importance only after 20 years. Thus, the choice of organism has an important influence on the course of science: not that our understanding would be completely different with a different model species, but there are many nuances that can only be observed in one, but not another species.

Finally, it should be noted that an interest in comparative studies should not be limited to naturalists and evolutionary biologists. Evolutionary comparisons tell us something about the model organism itself. They broaden the biological perspective and delineate the many roads nature can take.

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